

GEOPHYSICAL VARIABLES AND BEHAVIOR: LXXIX.
OVERT LIMBIC SEIZURES ARE ASSOCIATED WITH
CONCURRENT AND PREMIDSCOTOPHASE GEOMAGNETIC
ACTIVITY: SYNCHRONIZATION BY PRENOCTURNAL FEEDING¹

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Summary.—Approximately 35% of the variance (multiple $r = 0.59$) in the proportion of overt seizures (forelimb clonus) within a group of 35 chronically epileptic male rats during 65, daily 10-min. observation periods was significantly accommodated by the variations in the magnitude of the increased geomagnetic activity at the same time as the seizures and with activity during the previous midscotophase. The results supported the hypothesis that increased geomagnetic activity during specific subintervals of the circadian period suppresses the activity of the endogenous anticonvulsant melatonin and lowers the threshold for paroxysmal electrical seizures. The possibility of employing large populations of (limbic) epileptic patients as a network or a very large array of biomonitors for geomagnetic activity is considered.

All biological systems upon or near the earth's surface are immersed within the steady-state geomagnetic field. Time-variations within this field, whose amplitudes are approximately 0.1% to 1% of the static background intensity, occur frequently. Heterogeneous sensitivity to these subtle fluctuations may be dependent primarily upon relatively simple parameters which modulate the electrical lability within the brain. Limbic epilepsy, because it is characterised usually by significant and chronic decreases in the threshold for the types of paroxysmal discharges that progress to electrical seizures within the entorhinal cortices and subadjacent hippocampal-amygdaloid complex, meets the theoretical requirements for this sensitivity.

Several correlational studies have suggested that elevations in geomagnetic activity (defined as the amplitude of the variation around a steady-state baseline) are associated with increased rates of convulsions which are secondary to temporal lobe seizures (Rajaram & Mitra, 1981). Experiences considered to be strongly correlated with nonconvulsive electrical seizures within the hippocampal-amygdaloid complex such as hallucinations and bereavement apparitions [most of which occur within three days after the death of the person (Persinger, 1988)] are also more frequent during midnight and 0400 hr. (local time) if there is also a sudden increase in global geomagnetic activity (Persinger, 1988; Randall & Randall, 1991). The magnitude of the change in this natural stimulus, which is often reported as a gross average of

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the eight successive 3-hr. intervals of global indices, involved shifts of 10 to 40 nanoTesla (nT) particularly if the previous nights were geomagnetically quieter (average of 10–15 nT).

This researcher (cf. Persinger & Lafreniere, 1977) has been pursuing the neurophysical mechanisms by which geomagnetically induced alterations in thresholds for electrical seizures could occur. The current working hypothesis is that there are physical variables, correlated with, but not necessarily identical to, the changes in the general amplitude of geomagnetic activity, which influence the probability of the induction of electrical seizures. By a second mechanism the proliferation of these electrical seizures into motor centers would be observable as automatisms or convulsions. These seizures are more likely to occur during the nights. Thus the mechanism for the hypothesized interaction of geophysical and neurochemical variables must involve (1) peaks of efficacy during nocturnal periods and (2) sensitivity to experimentally produced magnetic fields which approximate geomagnetic fluctuations.

One possible mechanism involves the direct effect of increased geomagnetic activity upon the pineal organ's synthesis of the endogenous anticonvulsant: melatonin. According to Lerchl, Nonaka, and Reiter (1991) and Reiter and Richardson (1992) exposures of 45 min. duration during the mid-scotophase (late local night) to slow wave (1 min. on-1 min. off) magnetic fields (25 microTesla) is sufficient to reduce melatonin levels within the pineal organ by 20% and to suppress the activity of the synthesizing enzyme of melatonin by about 30%. The actual mechanism is very likely to involve some combination of (1) the cyclotron resonance effect (Lerchl, Reiter, Howes, Nonaka, & Stokkan, 1991) upon calcium due to the natural ratio of the amplitude of the geomagnetic variations relative to the steady-state field (approximately 1:100) and (2) the impedance matching between the temporal pattern (period structure) of the geomagnetic variations and the electrotonic characteristics of the *nervi conarii* (Quay, 1974) which are distributed like a neuronet within the pineal organ.

To pursue these neural mechanisms, a practical model which produced a chronic, stable increase in the probability of electrical seizures was essential. We (Bureau, Peredery, & Persinger, 1994) have found that rats in which acepromazine (30 mg/kg) was injected after limbic seizures were precipitated [by a single systemic injection of 3 mEq/kg of lithium chloride that is followed 4 or 24 hr. later by 30 mg/kg of pilocarpine (sub.cu.)], display intermittent spontaneous overt motor seizures (identical to Type IV and Type V electrically kindled seizures) over a period of several months. The occurrences of electrical seizures are inferred by brief periods of rearing, forelimb clonus, and then, about 30 sec. later a brief period of marked hyperresponsivity ("fear").

Histomorphological analyses of the brains of these rats indicate that neurons within several subcortical nuclei, including the amygdala within the forebrain are partially or totally damaged. The only aggregate which is not discernably affected qualitatively by light microscopy (400 X) within the amygdala is the central amygdaloid nucleus. Its major antagonists [abbreviations of Paxinos and Watson (1986) in parentheses], the basolateral ventral (BLV) nuclei and lateral anterior ventral nuclei (LAV) are always significantly damaged (Bureau, Peredery, & Persinger, 1994). Because one of the basic functional processes of an aggregate of neural elements which compose a system is mutual antagonism between subsets, one would expect a marked disinhibition of the central nucleus due to damage within the intrinsic neurons which typically maintain homeostasis. Consequently, neurons within the central nuclear group would be released from their normal inhibition. If the behavior of an animal at any given time is determined by those portions of the brain which are most active, then the behavioral correlates of the electrical stimulation of the central amygdaloid nucleus such as fear and enhanced startle to acoustic stimuli should predominate the behavioral profile (Liang, Melia, Campeau, Falls, Miserendino, & Davis, 1992). These precise behaviors have been observed (Persinger, *et al.*, 1993).

The central amygdaloid nucleus is also a major modulator of the epileptogenic neuropeptide, called corticotrophin releasing factor or CRF. A significant proportion of the corticotrophin releasing factor is localized within the parvocellular neurons of the paraventricular nuclei of the hypothalamus which, when stimulated, secrete this hormone and a variable quantity of arginine vasopressin. Their action upon the corticotropes of the anterior hypophysis cause an increased secretion of adrenocorticotrophic hormone or ACTH within seconds (Dallman, Akana, Bradbury, Strack, Hanson, & Scribner, 1994). This time frame is optimal for potential classical conditioning.

In the rat, which becomes active during the night, a slow rise in adrenocorticotrophic hormone and circulating corticosterone begins within a few hours before the onset of the active (night) period. The release of corticosteroid can be synchronized and superimposed upon the diurnal variation by delivering food to rats at the same or fixed time of day (Mistlberger & Rusak, 1988). We had found that the daily incidence of overt limbic motor seizures increase within 10 min. after introduction of a small amount of food into the cage if the chronic epileptic rats were given this food the same time each day for about five to ten successive days. This occurred even when the same food was available *ad libitum* through the foodhopper within the cage. The effect appeared to be intensified by the social facilitation (despite single-cage housing) related to the auditory feedback of several dozens of rats simultaneously eating hard food cubes within steel cages (unpublished observations).

The following experiment tested the most compelling behavioral prediction of this effect. If: (1) epileptogenicity is increased by the neuromorphological changes induced by the consequences of the lithium/pilocarpine injection, (2) the entrainment of the release of the corticotrophin releasing factor (as inferred by the synchronized release of adrenocorticotrophic hormone by routine feeding) or some strongly correlated neurochemical, increased the probability of the generalization of electrical seizures to motor sequences, (3) the disinhibition of neuronal activity mediated this process within the central amygdaloid nucleus, and (4) endogenous concentrations of melatonin suppress the generation of paroxysmal activity within the amygdala, then periods of enhanced geomagnetic activity should reduce the efficacy of the endogenous melatonin mechanism and hence be associated with increased incidence of electrical seizures (as inferred by forelimb clonus and fear responses) within 10 minutes of delivering a temporally fixed ("predictable") food stimulus. The weak geomagnetic effect would be amplified because the rats' thresholds for seizures would have been lowered *a priori* by the daily entrainment of (anticipatory) stimuli.

METHOD

To test the hypothesis that synchronized food delivery in free feeding, chronically epileptic rats should encourage the release of corticotrophin releasing factor and hence increase the incidence of seizures if the inhibitory influence of the normal levels of melatonin is suppressed by geomagnetic activity, a total of 35 male albino Wistar (Charles River, Quebec) rats were housed singly for 20 days before the observations began. Thirty of the rats were chronic epileptic animals; this condition had been induced about two months previously, when the rats were 90 days of age, by a single systemic injection of lithium chloride (3 mEq/kg) which was followed 4 hr. later by 30 mg/kg of pilocarpine and 30 min. later by 30 mg/kg of acepromazine. The other five rats served as controls for observational bias. Rats were identified by code numbers until the code was broken at the end of the study; the experimenter was not familiar with the condition of the animal. Food and water were freely available (*ad libitum*) throughout the study.

From 29 September, 1993 until the end of the study, two approximately 10-gm cubes of Purina rat chow were dropped into the cage of each rat between 1830 and 1900 hr. local time; the light:dark cycle was 12:12 hr. and (dark) began at 1930. From 3 October to the completion of this study, the numbers of rats per session that exhibited the conspicuous stereotyped rearing, rapid forepaw clonus, and either fear or clonic convulsion during the subsequent 10 min. (after the introduction of the food cubes) were recorded. A rat received a score of 0 or 1 for the occurrence of this behavior per day. As a behavioral referent, the occurrence of infrequent behaviors,

e.g., staring, circling, excessive vibrissae movements (whisker twitching) were also recorded for each rat. After about five days (3 October) of this procedure the rats engaged in marked, auditory group eating during the presentation of the two food pellets despite their single housing and the fact that food was available at all times.

The proportions of the rats displaying overt seizures and anomalous behaviors per day were calculated. The proportion was simply the percentage of chronically epileptic rats (identified at the end of the study) which displayed the behaviors. Proportions rather than total numbers were employed to estimate percentages of the sample population of epileptics which may be vulnerable to the geomagnetic correlates and because during the two months of observation, three rats died suddenly.

The daily global aa (average antipodal) index, which is an inference of geomagnetic activity (expressed in nanoTesla), as well as the daily 3-hr. Kp indices (semilogarithmic transformations of the magnitude of variation) were obtained from the Monthly Geomagnetic Bulletin (National Geophysical Data Center, 325 Broadway, Boulder, Colorado, 80303). Geomagnetic activities for the successive 3-hr. intervals of the day were obtained in light of the results by Yaga, Reiter, Manchester, Nieves, Sun, and Chen (1993) that the suppression of melatonin in response to the application of pulsed magnetic fields (1 min. on, 1 min. off) for 45 min. was significant when applied during the middle of the rats' night cycle or scotophase (beginning 0045 hr. or 0245 hr.) but not when applied during the early phase (beginning 2245 hr.). To ensure that geomagnetic activity was a primary source of association and not due exclusively to the strong coupling between solar activity and geomagnetic perturbations, the numbers of optical and x-ray solar flares per day were also recorded (Preliminary Report and Forecast of Solar Geophysical Data; Boulder, Colorado).

To accommodate the potential discrepancies due to the differences between local and universal time and the latency of response within the population of epileptic rats, lag/lead regression analyses were completed by employing lag 2 (2 days) of the proportions of overt seizures or infrequent behaviors per day and the 0 lag and lag 1 through 5 for the daily global average antipodal index and for the numbers of solar flares. This symmetrical lag/lead analysis allows potential entry into the equation of stimuli from days before, during, and after the behaviors. When causal relationships and not random inclusions or third factors are operative, the result is usually temporally asymmetric, i.e., only variables from before the behavior enter the equation.

To discriminate the contribution from more narrow increments of time during the 24-hr. period which contributes to the daily average, separate analyses were employed for each of the eight daily 3-hr. Kp indices. Because

regression assumes linearity, one-way analyses of variance (ONEWAY with POLYNOMIAL) for the proportion of seizures per day were completed as a function of the 3-hr. Kp values (which are expressed as a limited set of integers) to obtain the "optimal" functional relationship between the proportion of seizures and the quasilog increments of geomagnetic activity. The existence of significant nonlinear terms would imply a "threshold" effect (Persinger, 1995). All analyses were completed by SPSS software on a VAX 4000 computer.

RESULTS

During the observation period the mean (and standard deviation) per day for each variable were overt seizures 2.1 (3.0), anomalous behaviors 0.4 (1.0), average index of geomagnetic activity 29.2 (19.9), numbers of optical solar flares 3.1 (3.1), and numbers of x-ray flares 1.9 (2.7). Fig. 1 shows the mean daily index of geomagnetic activity (estimated planetary a values) and the percentage per day (range 0 to 15%) of the population of epileptic rats which exhibited the overt seizures during the 10-min. periods following the food stimulus. Lag/lead multiple regression indicated that 16% ($F_{2,60}=5.79$, $p<.01$) of the variance (multiple $r=0.40$) could be accommodated by the geomagnetic activity on the day of the observations ($\beta=0.32$) and the numbers of solar flares ($\beta=0.25$) two days before the observations. The results were similar after log (base 10) transformed a values; the only variables to enter the equation ($F=5.30$, $p<.01$) were the transformed geomagnetic activity of the day of the observation and the numbers of optical flares (but not numbers of x-ray flares, even after square-root transformation) two days before the increase in geomagnetic activity (multiple $r=0.40$). The daily variations in the percentages of rats displaying anomalous behaviors were not significantly associated with any of the geophysical variables.

Statistically significant associations occurred between the proportions of the epileptic rats which exhibited seizures and 3-hr. Kp values during specific intervals on the day of the observation. One-way analyses of variance indicated that the proportion of overt behaviors showed a statistically significant quadratic relationship with Kp values during only 0300 hr. to 0600 hr. UT ($F_{4,60}=15.85$, $p<.001$, $\eta^2=0.52$), 0600 to 0900 hr. UT ($F_{4,60}=12.50$, $p<.001$; $\eta^2=0.45$), and 2100 hr. to 2400 hr. UT ($F_{5,49}=14.41$; $\eta^2=.51$). Because local time during this period was four (Day Light Savings Time) to five hours (Eastern Standard Time) earlier, these periods were equivalent to 2200 hr. to 0200 hr., 0100 hr. to 0500 hr., and 1600 hr. to 2000 hr., respectively. Inspection of the means indicated that the proportions of rats displaying seizures (>5% of the population) were greater when the Kp value was 5 or greater for the second and eighth 3-hr. interval and 4 or greater for the third 3-hr. interval. There was no significant association between any of

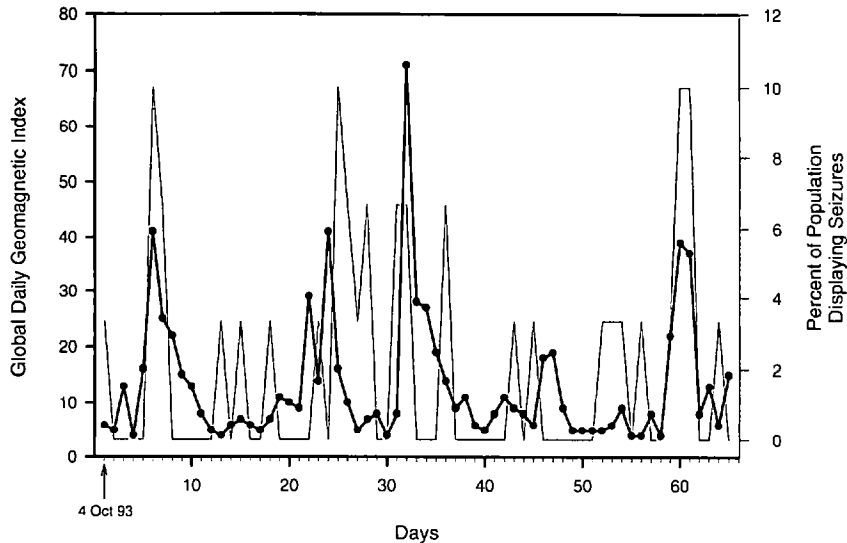


FIG. 1. Mean estimated planetary a index ($\times 2$ = approximate nT) and the percentage per day of chronic (limbic) epileptic male rats (horizontal line at zero on the gray scale indicates no seizures on that day) that displayed spontaneous overt limbic motor seizures in response to an anticipatory food stimulus

the daily 3-hr. increments of K_p values and the proportion of rats displaying anomalous behaviors ($F_{4,60} < 1.00$, $p > .05$).

Factor analyses of the eight K_p values per day indicated two factors; one was loaded primarily ($r > 0.70$) by the values during the first nine hours (eigenvalues = 5.79) of the day and a second factor (eigenvalue = 1.54) was loaded by values from the last six hours of the day. To assess the independence of the contribution of geomagnetic activity during the scotophase the night before the observations and the time of the feeding and to accommodate the nonlinearity of the effect, the values for the second and eighth daily 3-hr. K_p values were recoded so that 4 or less was equal to 0 and 5 or greater was equal to 1 while the values for the third interval were recoded so that 3 or less was equal to 0 and 4 or more was equal to 1. These transformations were based upon the results of the *post hoc* (Scheffé's test set at $p < .05$) and polynomial analyses.

Multiple regression analyses yielded a multiple R of 0.59 ($F_{2,62} = 15.56$, $p < .001$) which was composed of the interval associated with the time of the synchronized feeding, the eighth 3-hr. K_p value (partial slope = 3.14; beta = 0.37) and the previous night's mid- to late local scotophase, the third 3-hr. K_p value (partial slope = 2.99; beta = 0.37; constant = 1.08). When the numbers of (optical) solar flares (slope = 0.27) two days previously were allowed

to enter the equation, the multiple R increased to 0.65. Serial correlations (Spearman ρ) between the proportions of seizures per day as a function of day during the total observation period were not statistically significant for either overt seizures (-0.07) or anomalous behaviors (0.12).

To discern the specificity of the variables which entered the equation, symmetrical partial correlations were completed between the proportions of seizures per day, the two 3-hr. Kp values, the global daily (aa) values and the numbers of flares two days previously. The partial correlations between the proportion of overt seizures and Kp values during the third ($r=0.48$, 0.43) and eighth (0.51 , 0.42) increment remained significant after first removing the variance associated with the numbers of optical solar flares (first value in previous parentheses) and the daily geomagnetic activity (second value in previous parentheses), respectively. The association between the numbers of flares and seizures became statistically significant (partial $r=0.25$, $p<0.05$) only after daily global geomagnetic activity had been first removed. However, the association between the larger (daily) temporal increment of geomagnetic activity and the proportion of seizures was no longer significant after either Kp values for the third ($r=0.02$) or eighth (0.05) period were first removed.

DISCUSSION

Influence of Environmental or "Psychosocial" Factors

The results of this study are congruent with the hypothesis that environmental or "psychosocial" factors that influence anticipation or entrainment of the release of epileptogenic neuropeptides can facilitate the effect of elevated magnitudes in geomagnetic activity upon the neuroelectrical conditions which promote the generalization of these processes to overt stereotyped movements or convulsions. The fact that the geomagnetic activity at the time of the observation and during the inferred peak of the previous melatonin cycle were the most powerful and significant predictors suggests that temporal factors in geomagnetic variations may summate to decrease the threshold for seizures. Greater vulnerability of the suppression of nocturnal melatonin levels to the magnitude of geomagnetic activity during the mid-scotophase is compatible with the experimental evidence (Yaga, *et al.*, 1993).

The nonlinearity of the effect, as defined by the accommodation of about one-third of the variance in the proportion of daily seizures by employing the concept of a "threshold," was clearly evident in this study. The increase in daily proportion of overt seizures within this epileptic population occurred most reliably when the 3-hr. Kp values were equal to or greater than 4 or 5. These values are equivalent to intensity variations between 50 nT and 100 nT. Although these values are about 250 times less intense than the magnitude of the electromagnetic fields employed for one hour by Yaga,

et al. (1993) which reduced the levels of pineal melatonin by about 20%, geomagnetic perturbations occur for much longer periods of time.

Whether presentation of a weak electromagnetic stimulus for a longer period of time exhibits an effect comparable to a more intense electromagnetic stimulus presented for a briefer period of time is an empirical question. What is clear, however, is that the potential biological information contained within the complex fundamental periods and harmonics of geomagnetic activity far exceeds that of the simple 60-Hz magnetic field. Indices of amplitude ignore the fact that an extremely large population of different perturbations, each with distinct frequency profiles, could be inadvertently overincluded within the "same" index of magnitude.

Implications for Humans

This research was designed to help answer essential questions concerning human limbic epilepsy. Of the approximately 20% of epileptics who are refractory to medication, about 80% of these patients who have drug-resistant epilepsies exhibit structural anomalies within the amygdala, entorhinal cortex or hippocampus (Heinemann, Zhang, & Eder, 1993). The results of this study are theoretically congruent with our clinical observations and reports from temporal lobe epileptic patients (with likely foci within the hippocampal-amygdaloid regions) that the probability of an overt limbic seizure during the day is related to sleep disruptions and particularly the occurrence of unusually emotional and "meaningful" dreams during the previous night. Periods of rapid eye movement (REM) sleep are normally associated with correlative and transient decreases in circulating melatonin levels (Goldstein & Pavel, 1981). If the suppression of melatonin levels during dream sleep is a primary contributor to the heart's vulnerability to premature ventricular beats (Rosenblatt, Hartmann, & Zwilling, 1973) during this phase, then additional suppression of this serotonin derivative by increased geomagnetic activity may explain the sudden cardiac deaths that occur in populations of epileptic rats and humans (Persinger, 1995).

A delayed effect (from the previous night) would also be compatible with the observation that disruptions within the paraventricular hypothalamic nucleus [a major input for the central amygdaloid nucleus (LeDoux, 1994)] could enhance sensitivity to subsequent geomagnetic stimulation given the disruption of the suprachiasmatic (hypothalamic)-spinal cord circuit in the melatonin rhythm-generating system (Klein, Smoot, Weller, Higa, Markey, Creed, & Jacobowitz, 1983). There is also evidence that melatonin acts directly upon the human suprachiasmatic nucleus to influence circadian rhythms (Weaver, Stehle, Stopa, & Reppert, 1993). Such disruptions would be compatible with the frequent clinical observation of "jet-lag-like" symptoms that have been reported by patients who exhibit limbic epilepsy (par-

ticularly those with low-level, chronic thyroidal symptoms) during the two days which follow the onset of geomagnetic storms.

The results also suggest that perhaps groups of limbic epileptics, particularly those who are resistant to total suppression of seizures by anticonvulsant medication, could serve as biomonitors of sudden increases in geomagnetic activity. If one assumes that the average probability of the daily display of seizures by several thousands of epileptics is more or less constant, then the occurrence of specific trigger stimuli such as sudden increases in geomagnetic activity would behave as "precipitating stimuli" or zeitgebers that would recruit the most sensitive members of this "neuronet" into a shorter temporal increment. The resulting leptokurtic distribution of the incidence of seizures (cf. Persinger, 1980) would be statistically conspicuous and would involve a process that would be similar to the lunar effect upon parturition or the effects of a single paroxysmal volley upon a group of neurons which, without a zeitgeber, would discharge quasirandomly.

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Accepted June 9, 1995.